

J. Lederberg
Madison, Wisconsin
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Dr. Joseph Lein
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Syracuse, New York

Dear Joe:

I am still amusing myself trying to predict your reaction to my last week's proposal. I hope the interval means you are giving it deep thought rather than tearing your hair out about it.

While waiting to hear your reaction on that, there were just two points that I wanted to bring up:

1. In reading around the subject of last week's proposal, I tried to see what was known about the effect of vigorous chlorination on proteins, polypeptides etc. and, somewhat to my surprise, could find almost nothing on it. This has a good deal of bearing on the possibility of getting substitutions on carbon link hydrogen atoms. It would be rather astonishing if there has not been the same interest in modified proteins for industrial applications as there has been for example with modified starches, modified celluloses etc. Have you any idea what would happen in the reaction I just indicated or what would happen if the more reactive groups were previously blocked, say with acetyl? I don't doubt there would be substantial degradation, but from the point of view of the proposal this would hardly matter.

2. My second point is much more concrete. We have just realized that streptomycin-resistant protoplasts remain susceptible to the drug. This suggests that the genetic resistance is a function of the wall, which being impaired in the protoplast, allows streptomycin to inhibit the cell. This suggests another approach at one of the most vexing problems of chemotherapy, namely, streptomycin-resistant tubercle bacilli. My immediate suggestion to you is to rescreen all of the antibiotics that you have previously accumulated, regardless of their individual activity on wild type *Mycobacteria*, and test them for synergism with streptomycin against a streptomycin-resistant mutant. It is entirely plausible that an agent which would be inefficiently inhibitory by itself might efficiently impair the integrity of the wall to allow streptomycin to act. This, of course, would save for further therapeutic use one of the most important weapons in the treatment of tuberculosis.

We will be away between December 19th and 27th, which I mention just in case this would have any bearings on any of your plans. Otherwise, waiting to hear from you.

Yours sincerely,

Joshua Lederberg

P.S.

I have also written about the penicillin interaction with streptomycin to Gardner Middlebrook in Denver, hoping he might be stimulated to make a more intensive study of that specific possibility.

J.L.

JL:jlq